

REMARKS

Claims 1-53, 55 and 59 are pending in the subject application. Claims 6 – 8, 18, 18, 20, 26, 28, 30 – 32, 39 – 41, 47, and 48 have been amended. Claims 18 and 47 have been amended for clarification and for correcting typographical errors. Support for the amendments to the claims is found throughout the specification as filed and no new matter is presented by the amendments. Claim 56 - 58 have been canceled without prejudice.

Favorable reconsideration in light of the amendments and remarks, which follows is respectfully requested.

Applicants respond to the prior Office Action as follows.

1. Objections to the Specification

Applicants would like to thank the Examiner for the withdrawal of certain objections to the specification. The applicants would like to further clarify the Examiner's comments found at page 3, paragraph 6 of the office action. Applicants submit that dimerization occurs in the "in vitro" experiment because of the TE domain, which is described at least at page 6, paragraph 3 to page 9 paragraph as being operable to catalyze dimerization.

2. Claim Objections

Applicants would like to thank the Examiner for the withdrawal of certain claim objections. In this action, the Examiner has maintained objections to claim 18 for having two sentences. As suggested by the Examiner, the informality has been corrected.

Claims 28 – 33 were objected to as being in improper dependant form. Without acquiescing, applicants have amended claim 28 to clarify the dependence of the claim.

Accordingly, the objections to the claims should properly be withdrawn and the claims allowed.

3. 35 U.S.C. §112, 2nd Paragraph Rejections

The Applicants would like to thank the Examiner for the withdrawal of the rejection to claims 1-55 and 59; 18-27; 47-48, and 50-55; 28-33, 31 and 33; 33, 34-55; 34-55; and claim 59. The Examiner has maintained the rejection to claims 4 and 37 under 35 U.S.C. § 112, second paragraph, as being indefinite because the term "weakly-nucleophilic" is unclear. The term "weakly-nucleophilic" is a well known term in the art and is not unclear to one of ordinary skill in the art. For example, see "Organic Chemistry," Third Edition, Ed. John McMurry, Brooks/Cole Publishing Co., Pacific Grove, CA (1992), pages 369-374. McMurry discusses the variability of nucleophilicity, for example, some solvents are less reactive nucleophiles, i.e., weakly nucleophilic. McMurry discusses at length the parameters affecting the nucleophilicity of a solvent. Thus, this evidence suggests that the term "weakly nucleophilic" is clear to one of skill in the art.

Claims 6-8 and 39-41 stand rejected again under 35 U.S.C. § 112, second paragraph, as being indefinite because the phrases "about 5" and "about 7" in reference to the pH are unclear as to their scope. Without acquiescing and to advance prosecution, Applicants have amended the claims to delete the term about.

The Examiner has maintained the rejection of claims 10, 12-33, and 59 under 35 U.S.C. § 112, second paragraph, as being indefinite because the term "hydrocarbon" in Claims 10, 12,

18, and 59 is unclear. Applicants assert that the term in the claim is “hydrocarbon group” and not “hydrocarbon.” Applicants define “hydrocarbon group” on page 16 of the specification. Applicants are entitled to be their own lexicographer, and have chosen to do so, while adequately defining the term “hydrocarbon group” in the specification. See, e.g., *Renishaw PLC v. Marposs Societa' per Azioni*, 158 F.3d 1243, 1250, 48 USPQ2d 1117, 1121 (Fed. Cir. 1988) (“The other clear point provided by these two canons covers the situation in which a patent applicant has elected to be a lexicographer by providing an explicit definition in the specification for a claim term. In such a case, the definition selected by the patent applicant controls.”). Thus, the term “hydrocarbon group” is not unclear.

Claim 10 stands rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for describing linking the thioester and the nucleophile; however, the formula in the claim contains an ester, not a thioester. The applicants have corrected typographical error as suggested by the Examiner.

Claims 10, 28-33 and 54 stand rejected under 35 U.S.C. § 112, second paragraph, for using the phrases like "about 4 carbon atoms" and "about 10 heteroatoms" because they are unclear as to their scope. Without acquiescing and to advance prosecution, Applicants have amended the claims to delete the term about. Claims 12-33 stand rejected again under 35 U.S.C. § 112, second paragraph because the Examiner fails to see how “N-C₂-C₆alkanoylC₂-C₆aminoalkyl” is clear from the art and finds the “N” at the beginning of the name unclear.

The rejection is traversed.

The name "N-C₂-C₆alkanoylC₂-C₆aminoalkyl" is standard IUPAC nomenclature. The "N" defines the location of attachment to the aminoalkyl residue. Thus, the term "N-C₂-C₆alkanoylC₂-C₆aminoalkyl" is clear and understandable to one of ordinary skill in the art.

The rejection to claims 20 and 48 under 35 U.S.C. § 112, second paragraph has been maintained. The Examiner continues to assert the claim are indefinite because the limitations of the pH of the side chain, the phrase "about pH 7" is unclear as to its scope. Without acquiescing and to advance prosecution, Applicants have amended the claims to delete the term about.

Accordingly, the rejections to claims 1-55 and 59 under 35 U.S.C. § 112 should be deemed overcome and the claims found allowable.

4. 35 U.S.C. §112, 1st Paragraph Rejections

The Examiner has maintained the rejection of claims 1-55 and 59 under 35 U.S.C. 112 for containing subject matter which was not described in the specification. The Examiner asserts that claims are directed to methods of cyclizing compounds wherein few structural limitations are imposed with respect to the functional examples. For example, the Examiner asserts that the majority of the substrates used in the cyclization reactions are short peptides (Examples 3-21) or depsipeptides (Examples 22-23), but that the few examples describing the use of peptide substrates does not support the claimed genus so that one of skill in the art would be able to predict the structure of the substrates usable in the claims. Applicants respectfully traverse the rejection of claims 1-55 and 59.

Applicants respectfully point out that it is the entire specification that is used to

determine whether or not the written description requirement is met and not just the Examples disclosed in the specification. At page 6, line 17 to page 9, line 18 of the specification, other examples of substrates are given that fully describe and are commensurate with the scope of the claims. Not only are several examples given, they are described in terms of a generic structure, thus providing “common characteristics,” i.e., structural, physical and chemical characteristics of the claimed substrates. That is, the generic structures of the substrates provide common chemical and structural characteristics that adequately describe the substrates. In addition, the specification describes the substrates as having an “end group functionality of the natural substrate for the TE domain, thus describing the substrates functionally. Thus, one of skill in the art could predict the structure of a substrate useful in the methods. Accordingly, claims 1-55 and 59 are fully described and the specification meets the requirement of 35 U.S.C. 112.

Claims 34-55 remain rejected under 35 U.S.C. § 112, first paragraph because the Examiner asserts that although the genus of methods is discussed in the specification, there is no evidence that any representative species of such a large and varied genus, wherein the elongation step is repeated indefinitely, was in the possession of the inventors at the time of filing. The applicants respectfully traverse this rejection.

Claims 34 – 55 are not directed to methods wherein the elongation step is repeated indefinitely, by is repeated only “until the intermediate substrate is of sufficient length to undergo macrocyclization.” The specification supports this at least at page 10, third paragraph to page 11, first carry over paragraph, where the specification describes that “[a]dditional elongation reactions can occur as needed until the substrate dimer molecule or oligomer is sufficiently long...,” and “a pentapeptide substrate typically is not long enough to undergo

macrocyclization. Dissociation of the TE domain bound pentapeptide occurs by intermolecular nucleophilic attack of the N-terminal amine functional group from a second pentapeptide substrate to generate a decapeptide substrate dimer that has a sufficiently long linear backbone for TE domain protein catalyzed macrocyclization....” Thus, additional elongation reactions are disclosed and enable the claims. Accordingly, claims 34 – 55 are fully described under 35 U.S.C. § 112, first paragraph.

Claims 1-55 and 59 remain rejected under 35 U.S.C. § 112, first paragraph for not reasonably providing enablement for methods using any PKS TE domains with any substrate or methods using NRPS TE domains with any substrate. The Examiner asserts,

“[t]he instant specification describes TE domains as portions of polyketide synthases (PKSs) or non-ribosomal peptide synthetases (NRPS). The examples exclusively use NRPS TE domains; no PKS TE domains are used. The specification describes how excised TE domain a polyketide synthase, DEBS, does not promote cyclization (see specification page 3). No guidance is presented for the use of PKS TE domains, in particular for the substrates necessary for the use of PKS TE domains. The state of the prior art contradicts the claim that excised PKS TE domains promote cyclization. Thus, the predictability of using any substrate with an excised PKS TE domain is extremely low. For all these reasons, the instant claims are not enabled for using PKS TE domains.”

Applicants respectfully traverse this rejection.

Applicants’ specification is clearly enabled for the scope of the claims by disclosing multiple examples of TE domains appropriate to catalyze the macrocyclization reactions. There is no requirement that working examples be given for each and every embodiment. Applicants, however, provided evidence by the incorporation by reference of the Trauger, et al. reference, which is cited on page 11 of the specification. Trauger, et al. state that PKS systems can produce new polyketides and peptides. See page 216, 1st column of Trauger et al. In addition, as the

specification states at the top of page 8, substrate specificity of other excised TE domains can be determined by those skilled in the art by routine procedures. Routine procedures are not considered “undue experimentation” as the Examiner asserts. The Applicants then provide guidance to those skilled in the art as to how to select appropriate TE domains and their substrates. In addition, the specification provides many working examples of the claimed methods. Thus, under the Wands factors Applicants have fully enabled the scope of the claims because no undue experimentation is necessary, only routine procedures are needed to determine substrates; Applicants provide guidance in the specification as to how to choose TE domains and substrates; many working examples are presented; and those of skill in the art are considered highly skilled.

Accordingly, applicants request the withdrawal of these rejections and allowance of the claims.

5. 35 U.S.C. § 102 (a) Rejections

Claims 1-8 and 11 stand rejected under 35 U.S.C. § 102(a) as being anticipated by Trauger *et al.* (Peptide cyclization catalysed by the thioesterase domain of tyrocidine synthetase. Nature. Sept. 2000. 407:215-218). The Examiner considers Trauger *et al* to be “by others” because inventors Burkart and Schwarzer are not authors.

Applicants submit herewith a copy of the Rule 131 Declaration filed with the previous response that effectively antedates the Trauger, et al., literature publication. Thus, Trauger, et al., is not available as prior art under 35 U.S.C. §102(a) against the claims of the instant application.

The exhibits, which were inadvertently not included with the previous response are included herewith.

Accordingly, applicants request withdrawal of the rejections and allowance of the claims.

CONCLUSION

Applicants submit that all claims are allowable as written and respectfully request early favorable action by the Examiner. If the Examiner believes that a telephone conversation with Applicants' attorney would expedite prosecution of this application, the Examiner is cordially invited to call the undersigned attorney of record.

Respectfully submitted,

Date: March 16, 2005

Customer No. 21874



Stephana E Patton, Ph.D. (Reg. No.: 50,373)
EDWARDS & ANGELL, LLP
P.O. Box 55874
Boston, MA 02205
Tel. (617) 439-4444